The Use of Opioids for the Treatment of Pain in Palliative Care

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Disclosure

No conflicts of interest to disclose

Objectives

At the end of this presentation, the participant will be able to:

• Devise an opioid pain plan in a patient who is opioid naïve
• Safely titrate opioids for increased analgesia
• Define opioid rotation and know how to calculate equianalgesic dosing of common short acting opioid
• Identify the situations where there is an increased risk of unintentional overdose with the use of opioids in the treatment of pain

Case-Mr. Torrez

Mr. Torrez, 76 yo man, recently dx’d with Stage IV NSCLC with multiple bony metastases treated with NSAIDs with minimal relief. Adding dexamethasone provided minimal relief but he still c/o respirophasic pain 7/10 in his lateral left mid ribs and 9/10 pain in his right shoulder pain, especially with movement, and multiple areas of his thoracic spine even with lying down. These areas correspond with bony metastasis on CT. There is no evidence of impending cord compression. He has been placed on gabapentin but discontinued it due to feeling “drugged.” His exam is consistent with tumor related pain in these areas. His LFT’s are normal except albumin is 1.9 and his eGFR is 70. He is scheduled for radiation treatments to his shoulder and spine in a week.

PPS is 50%

He has been reluctant to take opioids due to worries about addiction but is willing to try them now. He is low risk for ADRB.
Mr. Torrez

What dose of opioid do you prescribe?

Increased risk of unintentional overdose

1. initiating opioid therapy
2. increasing dosage
3. opioid rotation

Common starting doses: opioid naïve patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult &gt;100kg: normal renal and liver function</th>
<th>Elderly or moderate renal or liver disease co-morbid conditions, polypharmacy, dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine PO</td>
<td>5 mg q4-6 hr pm</td>
<td>2.5 mg q6-8 hr pm</td>
</tr>
<tr>
<td>Oxycodone PO</td>
<td>5 mg q4-6 hr pm</td>
<td>2.5 mg q6-8 hr pm</td>
</tr>
<tr>
<td>Hydrocodone PO</td>
<td>5 mg q4-6 hr pm</td>
<td>2.5 mg q6-8 hr pm</td>
</tr>
<tr>
<td>Hydromorphone PO</td>
<td>1 mg q4-6 hr pm</td>
<td>0.5 mg q6-8 hr pm</td>
</tr>
</tbody>
</table>

Mr. Torrez

- you choose oxycodone 2.5 mg q 4 hr prn pain
- polyethylene glycol 17g/d
- consider antiemetic for nausea
- careful instructions to his wife who will be administering the medication
- see him back in 2 days (or call)
He calls your office the next day and says the pain is no better, 7-9/10
He is taking 5mg oxycodone every 4 hours

What dose do you prescribe now?

Increased risk of unintentional overdose

1. initiating opioid therapy
2. increasing dosage
3. opioid rotation

Titrating for improved analgesia

- If the patient has mild pain (1-3/10) while taking the prior regimen, consider no increase and addition of adjuvant medication or co-analgesic, but may increase by 10-25%
- If pain is at moderate level (4-7/10) on the prior regimen, may increase total dose by 25-50%
- If pain is severe (8-10/10) on the prior regimen, may increase total dose by 50-100%
- Most increases are 10-50%
- Do not increase by > 100%
Mr. Torrez

- Increase to 5 mg q 4-6 hr prn pain
- calls again next day, taking q 4 hr- slightly better, 7/10 but wants better analgesia
- When can you increase the oxycodone again?

Mr. Torrez

- steady state is reached after ~ five 1/2 lives for short acting (SA) agents if taken continuously
- SA agents have 1/2 life ~ 4 hours
- so may increase in 24 hours if needed

Mr. Torrez

- increase to 7.5 mg q 4 hr- pain is sightly better, increase again in 24 hr to 10 mg and his pain is 5/10—he can live with that
- but he has to wake up all night to take pills every 4 hours- not getting good rest
- ? long acting agents

Time course of SA and LA agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset</th>
<th>Peak Effect</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl IV</td>
<td>&lt; 1 min</td>
<td>&lt; 5 min</td>
<td>0.5 – 2 hr</td>
</tr>
<tr>
<td>IV Morphine</td>
<td>1-2 min</td>
<td>10 - 15 min</td>
<td>2 - 4 hr</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO – SA</td>
<td>20 – 30 min</td>
<td>60 - 120 minute</td>
<td>2-6 hr</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO – LA</td>
<td>Within 2 hr</td>
<td>PLATEAU 3 – 8 hr</td>
<td>8 – 12 hr</td>
</tr>
<tr>
<td>MS Contin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycontin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl Patch</td>
<td>13 – 24 hr</td>
<td>BROAD PLATEAU</td>
<td>48 – 72 hr</td>
</tr>
</tbody>
</table>
Mr. Torrez

Steps to convert short acting agent to long acting agent- morphine ER, oxycodone ER

1. total 24 hour use of opioids—> 10mg oxycodone q 4 hr= 60mg/24 hr
2. divide by 2 or 3 (q 12 or 8 hr dosing)—> 20mg q 8 hr or 30 mg q 12 hr (ATC, not prn)
3. consider breakthrough dose option

Mr. Torrez

- breakthrough pain dose—> 10% rule
- use 10% of total 24 hour dose as a break through dose
- use SA agents q 2-4 hr pm

Mr. Torrez

- oxycodone 20mg q 8 hr= 60 mg/24 hr
- BT = 6 mg (round down to 5mg) q 2-4 hr pm pain
- may use 5-15% if needed—> 2.5-10mg q 2-4 hr pm

He does well averaging 3 BT doses a day but must change to hydromorphone for insurance reasons—> opioid rotation
Increased risk of unintentional overdose

1. initiating opioid therapy
2. increasing dosage
3. opioid rotation

Opioid rotation

- NIH- interdisciplinary expert panel with clinical and research expertise in opioid pharmacology
- Definition:
  "Opioid rotation (or switching) is a change in opioid drug or route of administration with the goal of improving outcomes"

Opioid rotation

- Occurrence of intolerable adverse effects during dose titration
- Poor analgesic efficacy despite aggressive dose titration
- Problematic drug-drug interactions
- Preference or need for a different route of administration
- Change in clinical setting that suggests benefit from an opioid with different pharmacokinetic properties
- Financial or drug availability considerations

Opioid rotation-3 steps

1. opioid equivalency table
2. 25-50% automatic reduction
3. adjustment for severity of pain, other factors
Step 1  
Opioid Equivalency Table  
(equianalgesic dosing)

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg) IV/SQ</th>
<th>Dose (mg) Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Mr. Torrez  
opoid equivalency table  
1. total opioids used in 24 hr  
   • oxycodone ER 20 mg x 3 = 60 mg  
   • BT = 3 doses/24 hr x 5 mg = 15 mg  
   • total = 75 mg/24 hr  
2. \( \frac{x \text{ mg hydromorphone}}{75 \text{ mg oxycodone}} = \frac{7.5 \text{ mg hydromorphone}}{20 \text{ mg oxycodone}} \)  
   \( x = 28 \text{ mg hydromorphone/24 hr} \)

Step 2- automatic reduction  
Safety reduction of 25-50%- account for individual variability in genetics, physiology, incomplete cross tolerance  
28 mg hydromorphone x .5 = 14 mg

Step 3-adjustment for severity of pain  
> adjustment may be increase, decrease or no change (-30% to +30%) depending on  
   • pain severity  
   • other medical conditions- psychosocial factors, co-morbid conditions (organ impairment), polypharmacy, sedation, severe illness, dementia
Mr. Torrez

no psychosocial factors, renal or liver organ failure, polypharmacy, sedation, but PPS is 50%, albumin is 1.9 so decrease by 10%

- hydromorphone 14 mg/d x .1 = 1.4
- round to 2 mg
- hydromorphone 12 mg/24 hr
- 2 mg po q 4 hr ATC for pain
- breakthrough—> 10% rule
- 1 mg q 2 hr prn pain

Opioid rotation-3 steps

1. opioid equivalency table
2. 25-50% automatic reduction
3. adjustment for severity of pain, other factors

Mr. Torrez

gradual titrate upward to 3 mg q 4 hr ATC and breakthrough dose of 2 mg q 2 hr prn ~ 3 doses/24 hr

develops SBO due to intraperitoneal metastasis

severe nausea and vomiting—> admission

can’t take oral meds
Step 1
Opioid Equivalency Table
(equinanlgesic dosing)

<table>
<thead>
<tr>
<th>Short acting</th>
<th>Dose (mg) IV/SQ</th>
<th>Dose (mg) Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Mr. Torrez- Step 1
- hydromorphone 3 mg q 4 hr ATC = 18 mg/24 hr
- BT doses ~ 3/24 hr, 2 mg/dose = 6 mg/24 hr
- total 24 hr dose = 24 mg
  
  \[
  x \text{ mg IV hydromorphone} \times 1.5 \text{ mg IV hydromorphone} = 7.5 \text{ mg oral hydromorphone}
  
  x = \text{hydromorphone} 4.8 \text{ mg/24 hr}
  
Mr. Torrez Step 2 automatic reduction 25-50%

- hydromorphone 4.8 mg x .25 = 1.2 mg
- hydromorphone 4.8 mg - 1.2 mg = 3.6 mg

Mr. Torrez- Step 3 adjustment for severity of pain, other factors

- analgesia adequate—> no change
- hydromorphone 3.6 mg/d 24hr/d = .15 mg/hr
Mr. Torrez breakthrough pain

- breakthrough dosing for IV opioids—> use the hourly basal dose and order q 15"- 2 hr prn pain
- hydromorphone .15 mg q 15" prn pain

Mr. Torrez IV route

- How often can I increase the basal rate?
  -q 24 hr
- How often can I change the prn (PCA, breakthrough) dose?
  -generally-hourly
  -in a pain crisis—>q 15"

Fentanyl Patches

- Fentanyl patches are good for chronic stable pain.
- They should not be prescribed to an opioid naïve patient.
- They are not good for rapidly escalating pain since they are very difficult to titrate!
  - Take 13-24 hours after application to become effective and 3 days to change dose....
  - Similarly, when a patch is removed, it takes 13-24 hours to be eliminated from the system
- ALWAYS educate patients and families about the 13-24 hour onset and appropriate usage
  - Ex. You can’t cut a patch, you can’t take it off and put it back on, etc.

Fentanyl patch dosing

- Converting oral morphine equivalent (OME) to fentanyl transdermal-increased risk of unintentional overdose
  - don’t guess
  - package insert, search on internet
  - factor built in to conversion chart, very conservative
Morphine (mg/day) DURAGESIC® Dose (mcg/h)

<table>
<thead>
<tr>
<th>Morphine (mg/day)</th>
<th>DURAGESIC® Dose (mcg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-134</td>
<td>25</td>
</tr>
<tr>
<td>135-224</td>
<td>50</td>
</tr>
<tr>
<td>225-314</td>
<td>75</td>
</tr>
<tr>
<td>315-404</td>
<td>100</td>
</tr>
<tr>
<td>405-494</td>
<td>125</td>
</tr>
<tr>
<td>495-584</td>
<td>150</td>
</tr>
</tbody>
</table>

+ Converting fentanyl transdermal to OME use 1:2

Methadone

- Very tricky, needs close monitoring
- High individual to individual variation in metabolism, half life varies 5 → 100 hr
- Liver reservoir
- QT interval prolongation- potent inhibitory effects on the human ether-a-go-go related gene (hERG) cardiac channel which can cause QTc interval prolongation
- Dose adjusted only every 5 days (for some- weeks)
- Many drug/drug interactions

→ If you initiate methadone for pain, strongly consider guidance from a pain specialist

Methadone- NIH expert panel guidelines

- <40–60 mg/d OME or opioid naive patient:
  - start methadone at 2.5 mg q 8 hr
  - initial dose increases of no more than 5 mg/d every 5 to 7 days
  - when 30 mg/day reached- may increase 10 mg/d q 5-7 days
- > 60 mg/day OME to methadone:
  - reduce dose by 75 to 90% of calculated equianalgesic dose or use 7% of OME
  - not > 30 to 40 mg/d initial dose
  - increases of no more than 10 mg/d every 5 to 7 days

Methadone

- obtain an ECG prior to initiation of methadone May use methadone if QTc <450 ms
- The panel recommends that clinicians consider alternate opioids in patients with a baseline QTc interval >450 ms but <500 ms
- If methadone is considered in a patient with a baseline QTc interval >450 ms but <500 ms, the clinician should evaluate for and correct reversible causes of QTc interval prolongation before initiating methadone
- risk factors for QTc interval prolongation
  - hypokalemia or hypomagnesemia
  - use of drugs with QTc-prolonging properties- various antiarrhythmics, antipsychotics, citalopram, tricyclic antidepressants, fluoroquinolones, and cisapride
  - impaired liver function
  - structural heart disease (congenital heart defects, history of endocarditis, heart failure)
  - genetic predisposition (congenital prolonged QT syndrome, familial history of prolonged QT syndrome)
- The panel recommends against use of methadone in patients with a baseline QTc interval >500 ms (strong recommendation, low quality evidence)
### Opioid Side Effects and Treatments

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Duration</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSTIPATION</td>
<td>Chronic</td>
<td>Bowel stimulant-polyethylene glycol 17 gm/d +/- senna 1-8 q us (not just fiber)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>3-7 days</td>
<td>prochlorperazine, promethazine, metoclopramide, ondansetron</td>
</tr>
<tr>
<td>Sedation</td>
<td>2-3 days</td>
<td>Decrease opioid dose, look for other causes as well</td>
</tr>
<tr>
<td>Pruritis/Itching</td>
<td>&lt;5 days</td>
<td>Anti-histamine, steroids</td>
</tr>
<tr>
<td>Confusion/Hallucination</td>
<td>&lt;2 days</td>
<td>lower dose opioid rotation</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td></td>
<td>Decreased respiratory rate &lt; 6/min NALOXONE preceded by sedation, miosis</td>
</tr>
</tbody>
</table>

### Sedation

Sedation- *may or may not* be caused by opioid

- renal or hepatic dysfunction
- other drugs- other opioids, benzodiazepines, alcohol, sedative-hypnotics, antispasmodics, antihistamines, seizure medications
- opioid toxicity- sedation, miosis, respiratory depression

### Additional recommendations

- Avoid polypharmacy of different opioids
- Avoid opioids as combination products- concern for toxicity of non-opioid component (acetaminophen, ibuprofen)
- Maximum acetaminophen = 3 grams, elderly < 2 grams
- AGA-commissioned poll
  - >1,000 U.S. adults aged 30 and older
  - 43 percent of chronic pain sufferers knowingly ingested more than the other recommended dose of over-the-counter pain medicine

### Additional recommendations

General Guidelines: *Start low and go slow, observe; adjust over time*

If you are treating pain, and it is not getting better

- right drug (adjuvant?)
- right amount
- non-physical component to the pain

*Total Pain*-physical, psychological, social, spiritual, existential sources of pain
Opioid Use in Renal Dysfunction and Dialysis

See the text following these summary tables for further information.

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Recommended Use</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Use cautiously, adjust dose as appropriate. **</td>
<td>Metabolites can accumulate causing increased therapeutic and adverse effects.</td>
</tr>
<tr>
<td>Hydromorphone/</td>
<td>Use cautiously, adjust dose as appropriate. **</td>
<td>The 3-glucuronide metabolite can accumulate and cause neuro-excitatory effects.</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Use cautiously, with careful monitoring; adjust dose if necessary. **</td>
<td>Metabolites and parent drug can accumulate causing toxic and CNS-depressant effects.</td>
</tr>
<tr>
<td>Codeine</td>
<td>Do not use.</td>
<td>Metabolites can accumulate causing adverse effects.</td>
</tr>
<tr>
<td>Methadone*</td>
<td>Appears safe. **</td>
<td>Metabolites are inactive.</td>
</tr>
<tr>
<td>Fentanyl*</td>
<td>Appears safe; however, a dose reduction is necessary. **</td>
<td>No active metabolites and appears to have no added risk of adverse effects; monitor with long term use.</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Do not use.</td>
<td>Metabolites can accumulate causing increased risk of adverse effects.</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Do not use.</td>
<td>Metabolites can accumulate, and use in renal dysfunction has been associated with hypoglycemia, cardiac conduction problems, and CNS and respiratory depression (Aminfar et al. 1989; Davies 1996; Kurella 2003; Shah et al. 2008).</td>
</tr>
</tbody>
</table>

* Negligible or no active metabolites; although, not considered first-line therapy. ** See Table below for dosing recommendations.

Recommended Use of Selected Opioids in Dialysis Patients (Arnoff 1998; Dean 2004)

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Recommended Use</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Use cautiously and monitor patient for rebound pain effect or do not use.</td>
<td>Both parent drug and metabolites can be removed with dialysis; watch for &quot;rebound&quot; pain effect.</td>
</tr>
<tr>
<td>Hydromorphone/</td>
<td>Use cautiously and monitor patient carefully for symptoms of opioid overdose.</td>
<td>The parent drug can be removed, but metabolite accumulation is a risk.</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Do not use.</td>
<td>No data on oxycodone and its metabolites in dialysis.</td>
</tr>
<tr>
<td>Codeine</td>
<td>Do not use.</td>
<td>The parent drug and metabolites can accumulate causing adverse effects.</td>
</tr>
<tr>
<td>Methadone*</td>
<td>Appears safe. **</td>
<td>Metabolites are inactive, but use caution because parent drug is not dialyzed.</td>
</tr>
<tr>
<td>Fentanyl*</td>
<td>Appears safe. **</td>
<td>Metabolites are inactive, but use caution because fentanyl is poorly dialyzable.</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Do not use.</td>
<td>Few data on meperidine and its metabolites in dialysis; risk of adverse effects.</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Do not use.</td>
<td>Propoxyphene is not dialyzed. Metabolites can accumulate causing increased risk of hypoglycemia, cardiac conduction problems, and CNS and respiratory depression (Aminfar et al. 1989; Davies 1996; Kurella 2003; Shah et al. 2008).</td>
</tr>
</tbody>
</table>

* Use caution because these drugs are not dialyzable.

Recommended Dosage Adjustments for Select Opioids in Renal Insufficiency (Arnoff 1999)

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>Morphine</th>
<th>Hydromorphone or Hydrocodone</th>
<th>Oxycodone</th>
<th>Methadone</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100*</td>
<td>50 to 100*</td>
<td>100*</td>
<td>100*</td>
<td>100*</td>
</tr>
<tr>
<td>10-50</td>
<td>50 to 75*</td>
<td>50*</td>
<td>50*</td>
<td>75 to 100*</td>
<td>75 to 100*</td>
</tr>
<tr>
<td>&lt;10</td>
<td>25 to 50*</td>
<td>25*</td>
<td>Do not use</td>
<td>50 to 75*</td>
<td>50*</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate. * = % of normal dose. Codeine, meperidine, and propoxyphene are not recommended for use.

Recommended Use of Opioids in Hepatic Dysfunction

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Recommended Usage</th>
<th>Comment</th>
<th>Dosing Recommendations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Use cautiously and monitor patient for sedation.</td>
<td>In severe hepatic impairment, the parent drug may not be readily converted to metabolites.</td>
<td>Increase the dosing interval by twice the usual time period.</td>
</tr>
<tr>
<td>Hydromorphone/</td>
<td>Use cautiously and monitor patient carefully for symptoms of opioid overdose.</td>
<td>In severe hepatic impairment, the parent drug may not be readily converted to inactive metabolites.</td>
<td>Decrease initial dose by 50% of the usual amount.</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Use cautiously and monitor patient carefully for symptoms of opioid overdose.</td>
<td>In severe hepatic impairment, the parent drug may not be readily converted to inactive metabolites.</td>
<td>Decrease initial dose by 1/2 to 1/3 of the usual amount.</td>
</tr>
<tr>
<td>Codeine</td>
<td>Avoid use.</td>
<td>In severe hepatic impairment, codeine may not be converted to the active metabolite, morphine.</td>
<td>—</td>
</tr>
<tr>
<td>Methadone</td>
<td>Not advised.</td>
<td>Not advised in severe liver failure due to risk of methadone accumulation.</td>
<td>—</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Appears safe; generally no dose adjustment necessary.</td>
<td>Decreased hepatic blood flow affects metabolism more than hepatic failure.</td>
<td>Dosing adjustment usually not needed.</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Do not use.</td>
<td>Inactive metabolite is associated with risk of seizer.</td>
<td>—</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Do not use.</td>
<td>Hepatotoxicity reported with or without acetaminophen component.</td>
<td>—</td>
</tr>
</tbody>
</table>

*Recommended dose in severe hepatic impairment.
References

- AGA survey shows chronic pain patients at risk of overusing OTC pain medications, Healio, Gastroenterology, January 26, 2016

References

- Paschls Z. Acute Pain Management for Inpatients with Opioid Use Disorder. AJN, September 2015; 115(9): 24-32
- Buprenorphine. palliativedrugs.com newsletter November/December 2006, BNF 4 7 2

References